1 570 374

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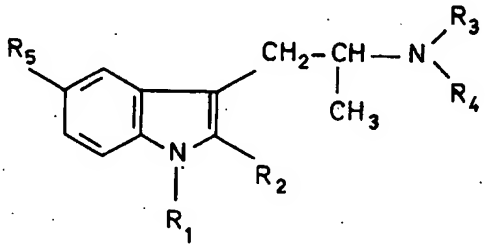
(54) INDOLES

(71) We, LABORATOIRES SAUBA S.A., a French Body Corporate of 260 rue de Rosny, 93104 Montreuil, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to therapeutic substances piperazino-3-indoles; a method of preparing them, and the therapeutic applications of these substances.

Some known indole derivatives have pharmacological properties, *inter alia* indole amines having the following general formula:

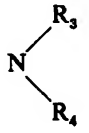


in which:—

R_1 represents a lower alkyl, a phenyl without a substituent, a phenyl bearing a halogen atom or a nitro group, a lower amino or alkoxy, a pyridyl, benzyl, lower benzyl alkoxy, halogeno benzyl or a hydrogen atom, when R_2 is a phenyl;

R_2 represents H, a methyl or phenyl;

R_3 and R_4 each denote a hydrogen atom or lower alkyl or



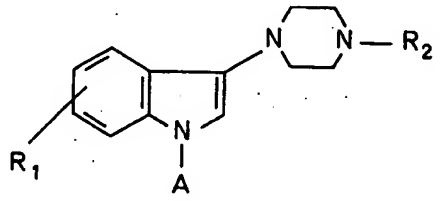
represents the radical of a cyclic amine having 5 or 6 atoms in the ring and another hetero-atom if required, more particularly a pyrolidine, piperidine, morpholine or N-methyl piperazine radical, and

R_5 represents H, F, Cl or OCH_3.

In these derivatives, the nitrogen atom of the amine is not directly fixed to the indole ring. The derivatives mainly have analgesic properties.

According to the invention, novel indole derivatives have been discovered and have different therapeutic properties from the aforementioned known derivatives.

According to the invention, the derivatives are piperazino-3-indoles having the following general formula:



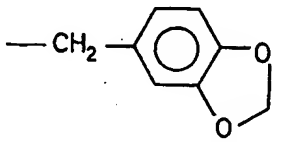
wherein:

A is a hydrogen atom, a carboxylic acid radical or an alkyl, dialkylaminoalkyl, benzyl or phenyl group, which may or may not be substituted,

R_1 is a hydrogen or chlorine atom or an alkyl group having less than five carbon atoms, methoxy or hydroxy group, and

R_2 is an alkyl, benzyl or phenyl group or a cyclic or heterocyclic group, which may or may not be substituted.

Preferably, the piperazino-3-indoles according to the invention are chosen either from the group of 3-piperonyl piperazino-indoles wherein R_2 is a piperonyl radical:



or from the group containing 3-alkylpiperazino-indoles, 3-benzylpiperazino indoles, 3-phenylpiperazino indoles and 3-cyclohexylpiperazino-indoles. The radical A can be chosen from a number of substitution radicals such as acetyl, benzyl, phenyl, methyl, ethyl or diethylaminoethyl. The phenyl radical can be a substituted derivative, e.g. a methoxyphenyl or trifluoromethylphenyl.

Radical R_1 can be a methoxy radical or a chlorine atom.

The following piperazino-3-indoles are preferred according to the invention;

1-acetyl 3 piperonylpiperazino indole,
1-benzyl 3 piperonylpiperazino indole,
1-acetyl 5 chloro 3 piperonylpiperazino indole,
1-acetyl 5 methoxy 3 piperonylpiperazino indole,
5-methyl 3 piperonylpiperazino indole,
1-ethyl 3 piperonylpiperazino indole,
1-acetyl 3 benzylpiperazino indole,
1-acetyl 30 methoxyphenylpiperazino indole,
1-acetyl 3 m. trifluoromethylphenylpiperazino indole,
1-N diethylaminoethyl 3 m. trifluoromethylphenylpiperazino indole,
5-chloro 3 methylpiperazino indole,
5-chloro 3 cyclohexylpiperazino indole,
1-phenyl 5-chloro 3 methylpiperazino indole, and
1-phenyl 5 chloro 3 cyclohexylpiperazino indole.

The invention also relates to salts of pharmaceutically acceptable acids of piperazino-3-indoles according to the invention, more particularly hydrochlorides, iodomethylates and maleates, the hydrochlorides being generally preferred.

Table I hereinafter gives the structural formula and names of some derivatives according to the invention.

Table II hereinafter gives some physical and chemical properties (i.e. the preparation yield, melting point, main absorption bands in the infra-red (IR in KBr)

and elementary analysis) for certain derivatives according to the invention.

The invention also relates to a method of preparing piperazino-3-indoles according to the invention.

In one version of the method, a substituted or non-substituted 3-indolinone is reacted with a piperazine derivative in an inert solvent.

Indolinones used as synthesis intermediates are prepared by known methods. The preparation of N-acetylindolinones has been described by C. D. NENITZESCU and D. RAILEANU, Chem. Ber. 1141, 1958 and the preparation of N-phenylindolinones has been described by P. FRIEDLANDER and K. KUNTZ, Chem. Ber. 1597, 1922.

The following are some non-limitative examples of preparing derivatives according to the invention.

EXAMPLE I.

1 acetyl 3 m. trifluoromethylphenylpiperazino indole (Compound No. V in Table I)

50.6 g (0.22 mol) of metatrifluoromethylphenylpiperazine was added to a solution of 35 g (0.2 mol) of N-acetyl-3-indolinone in 200 ml of dry toluene in a nitrogen atmosphere. The reaction mixture was refluxed in the presence of para-toluene sulphonic acid (0.500 g) for 24 hours, the water being removed as it was formed during the reaction. Next, the solvent was evaporated at reduced pressure and the crystalline residue was dissolved in 250 ml of boiling ethanol. In this manner, 54.7 g of the desired product was separated.

M.P. = 148° (methanol). Yield = 70%

IR(KBr): 2860, 1690, 1620 cm^{-1}

$C_{21}H_{20}N_3OF_3$ = 387.4

Calc. C: 65.10 H: 5.20 N: 10.84

Found C: 64.95 H: 5.10 N: 10.88

Hydrochloride of the aforementioned derivative:

Gaseous hydrochloric acid dissolved in ethanol was added to a suspension in 80 ml ethanol of 8 g of the derivative obtained according to Example I. The acid was added in the amount necessary to obtain complete dissolution. After agitation for 1 or 2 hours, the hydrochloride crystallized and 7.4 g of the product was separated. Yield = 87%.

EXAMPLE II.

1 acetyl 3 piperonylpiperazino indole (Compound No. III)

35 g (0.2 M) of N acetyl-3-indolinone was dissolved in 200 ml toluene and 53 g (0.22 M) piperonylpiperazine was added. The mixture was refluxed for 24 hours in the presence of para-toluene-sulphonic acid (0.5 g) the water being separated as soon as it was formed. Treatment was as in Example I, the solvent being driven off.

The residue was dissolved in ethanol hydrochloride and the monohydrochloride was crystallized out.

Weight: 52 g. Yield: 55% MP = 250°C

IR (KBr): 3100, 2400, 1685, 1610 cm^{-1}

$C_{22}H_{23}N_3O_3$, HCl – 413.9

Calc. C: 63.84 H: 5.86 N: 10.15

Found C: 63.95 H: 5.93 N: 10.13

EXAMPLE III.

3 piperonylpiperazino indole (compound No. XIII in Table I)

25 g soda in 50 ml water was added to a solution in 150 ml ethanol of 25 g (0.06 mol) of hydrochloride obtained as in Example II. The mixture was boiled for 90 minutes. The solution was cooled and poured on to iced water. 13.5 g of 3 piperonylpiperazino indole was separated.

Yield = 66% M.P. = 155° (ethyl acetate-ethanol)

IR (KBr): 3300, 3400, 2810, 1620 cm^{-1}

$C_{20}H_{21}N_3O_2$ = 335.4

Calc. C: 71.62 H: 6.31 N: 12.53

Found C: 71.53 H: 6.21 N: 12.39

EXAMPLE IV.

3-m. trifluoromethylphenylpiperazino indole (Compound No. XIV)

Yield = 89% M.P. = 154° (ethanol)

IR (KBr): 3400, 3260, 2840, 1610 cm^{-1}

$C_{19}H_{18}N_3F_3$ = 345.3
Calc. C: 66.07 H: 5.25 N: 12.16
Found C: 66.05 H: 5.19 N: 12.12

Dihydrochloride of compound No. XIV:
IR (KBr): 3400, 2500, 2400, 1620 cm^{-1}
Analysis by anhydrotitrimetry
$C_{25}H_{31}N_4F_3$, 2HCl, H_2O = 535.

EXAMPLE V.

1 benzyl 3 piperonylpiperazino indole (Compound No. XV in Table I)

A suspension of 3.35 g (0.01 mol) of the product obtained as in Example III and 1.24 g (0.011 mol) of potassium tertiobutylate in 20 ml distilled HMPT cooled to 0°C was agitated for 90 minutes in a nitrogen atmosphere. A solution of 1.26 g benzyl chloride in solution in 5 ml HMPT was added dropwise to the first solution, which was kept at 0°C.

Agitate at the same temperature for 60 minutes and pour on to 100 ml iced water. The precipitate was dissolved in a few millilitres of ether and separated, giving 4 g of product.
Yield = 94% MP = 124° (ethanol)
IR (KBr): 2830, 2790, 1610 cm^{-1}
$C_{27}H_{27}N_3O_2$ = 425.5
Calc. C: 76.21 H: 6.40 N: 9.88
Found C: 76.20 H: 6.39 N: 10.21

EXAMPLE VI.

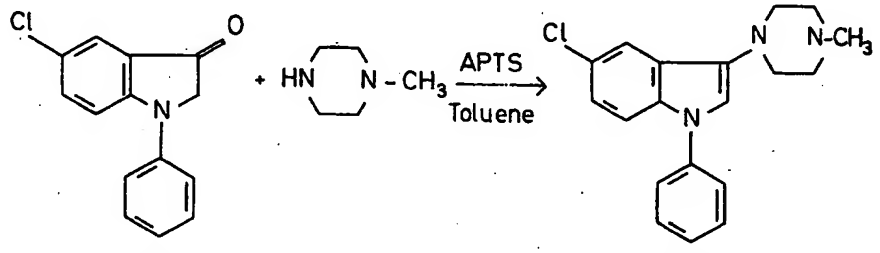
1 N diethylaminoethyl 3 m. trifluoromethylphenyl piperazino indole (Compound No. XVI in Table I).

The method was as in Example V, using diethylaminoethyl chloride and 1-acetyl 3 piperonylpiperazino 2-3 dihydro indole.
Yield = 60% of crystalline product. MP <50% (purification by chromatography on an alumina column).

EXAMPLE VII.

1 phenyl 5 chloro 3 methylpiperazino indole (Compound No. XIX in Table I).

The reaction was similar to that between secondary amines and N acetylindolines, i.e. 1-phenyl 5-chloro 3-indolinone was reacted with methyl piperazine in accordance with the following equation:



Place the following in a 250 ml three-necked flask under nitrogen, fitted with an agitator and a condenser:

3 g of 5 chloro N phenylindolinone
2.7 g of N methyl piperazine
50 ml distilled toluene and
APTS (added several times during refluxing)
Cool, concentrate to dryness.

Send through a neutral alumina column (180 g), eluting with benzene and then with a mixture of benzene and methylene chloride. 1 g of pure product is obtained.
MP = 171°C. Yield = 23%
IR: 2810 cm^{-1} N—CH_3
1600 cm^{-1} aromatic
no C = O no N = H

950 mg was converted into the hydrochloride in ethyl alcohol, using a mixture of ethyl alcohol and hydrochloric acid. 750 mg of slightly pink hydrochloride was obtained. MP <250°C.

EXAMPLE VIII.

1 phenyl 5 chloro 3 cyclohexylpiperazino indole (Compound No. XX)

1 g of 5 chloro 3 cyclohexylpiperazino indole (Compound No. XVIII), 20 ml bromobenzene, 1.4 g iodobenzene, 3.2 g anhydrous K_2CO_3 and 1.75 g powdered copper were poured into a 100 ml three-necked flask under nitrogen, with agitation. The mixture was refluxed for 24 hours, separated when cold, concentrated, conveyed through a neutral alumina column (50 g) and eluted with methylene chloride. 300 mg of base was obtained.

MP = 165°C. Yield = 24%

IR (KBr): 2940, 2860, 2820, 1600 cm^{-1}

Absence of NH

Analysis: $C_{24}H_{28}ClN_3$ M = 393.5

Calc. C: 73.20 H: 7.12 N: 10.68

Found C: 72.84 H: 7.28 N: 10.52

The invention also relates to the medical and veterinary use of piperazino-3-indoles according to the invention and their pharmaceutically acceptable salts, *inter alia* hydrochlorides.

The following are the results of pharmacological tests made on the derivatives according to the invention.

1) *Toxicity*

The importance of the derivatives according to the invention is that they all have very low toxicity — i.e. the LD_{50} is greater than 600 mg/kg per os in the mouse, i.e. is impossible to determine.

The pharmacological research was based on the following tests:

Acute toxicity in the mouse:

This was evaluated from the observed death rate during 48 hours of batches of 4 animals at each dose administered.

The doses were administered in geometrical progression, doubling from 100 to 1600 mg/kg.

2) *Sedative activity*

Actimetry in the mouse:

This test was made by the method described by J. R. BOISSIER and P. SIMON, "Action of caffeine on the spontaneous motility of the mouse" (Arch. Int. Pharmacodyn., 1965, 158, 212—221).

Twenty minutes after the test product had been administered to batches of 12 animals per dose, the mice were placed in actimeters comprising individual photoelectric cells. The number of spokes travelled in 5 minutes was counted.

The activity of the product at each dose was expressed as a percentage increase or reduction in the exploration reaction, calculated by the following formula:

$$1) - \frac{\text{Average number of spokes travelled by the treated mice}}{\text{Average number of spokes travelled by the controls}} \times 10$$

The ED_{50} was graphically evaluated, based on these results.

3) *Analgesic activity*

SIEGMUND test with phenylbenzoquinone in the mouse:

This test was made by the method described by E. SIEGMUND, R. CADMUS and G. LU, "A method for evaluating both non-narcotic and narcotic analgesics" (Proc. Soc. Exp. Biol. Med., 1957, 95, 729—731).

Thirty minutes after the test product had been administered to batches of 12 animals per dose, phenylbenzoquinone in 0.02% solution in water containing 5% ethyl alcohol was intra-peritoneally injected, the amount being 0.25 ml per 20-g mouse.

A count was made of the wriggles by each animal between 5 and 10 minutes

after injection of phenylbenzoquinone.

The activity of each dose of product was expressed as a percentage protection, calculated from the following formula:

$$1 - \frac{\text{Average number of wriggles by treated rats}}{\text{Average number of wriggles by controls}} \times 100$$

The ED_{50} was graphically evaluated from these results.

4) *Anti-inflammatory activity*

Carrageenin oedema in the rat determined by the method described in C. A. WINTER, E. A. RISLEY and G. W. NUSS "Carrageenin-induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs (Proc. Soc. Exp. Biol. Med., 1962, *111*, 544—547).

One hour after the test product had been adminstered to batches of 6 animals per dose, oedema was brought about by injecting 0.05 ml of a 1% carrageenin suspension in physiological serum into the left plantar aponeurosis.

The volume of the paw was measured by plethysmography before the oedema had been produced (V_o) and three hours afterwards (V_3).

The activity of each dose of product was expressed as a percentage protection, calculated from the following formula:

$$1 - \frac{V_3 - V_o \text{ in the treated rats}}{V_3 - V_o \text{ in the control rats}} \times 100$$

The activity of the product relative to 60 mg/kg phenylbutazone was expressed as a percentage calculated from the following formula:

$$\frac{V_3 - V_o \text{ for the product}}{V_3 - V_o \text{ for 60 mg/kg phenylbutazone}} \times 100$$

Interaction in vitro with serotinin in the uterus of a female rate in oestrus. This test was made by the method described in J. M. GADDUM and K. A. HAMEED, "Drugs which antagonize 5-hydroxytryptamine" (Brit. J. Pharmacol., 1954, *9*, 240—248).

An attempt was made to find that concentration of the test product which, when previously added in the bath, produced a 50% reduction in the concentration caused by the antagonist.

Antipyretic activity in the rabbit.

Hyperthermia was produced in rabbits by intravenous injection of 0.6 ml of Professor Pierre Delbet's stock-vaccine broth.

The test product was orally administered two hours later to batches of two rabbits.

The rectal temperature was measured 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after administration.

The rectal temperature curve was compared with that for the controls.

The results of these pharmacological tests are given in Table III hereinafter. The results are expressed in mg/kg of live weight for the LD_{50}, the actimetry test and the analgesic test measured by the test with phenylbenzoquinone. The results are expressed relative to phenyl butazone when measuring the anti-inflammatory activity, Harmine when measuring the anti-serotonin activity, and aspirin when measuring the anti-pyretic activity.

The aforementioned pharmacological test results show that piperazine-3-indoles according to the invention have remarkable anti-inflammatory and analgesic properties.

Derivative IV, which has low toxicity, is a strong analgesic and has an anti-inflammatory effect equal to phenylbutazone, is mainly indicated for treatment of painful rheumatism.

Derivative X, which has the same analgesic activity but only a slight anti-inflammatory effect, is preferably used as an analgesic. It is also indicated in certain forms of migraine, owing to its anti-serotonin activity.

Derivative XI, which has very low toxicity, a considerable analgesic and anti-

inflammatory effect and an interesting anti-pyretic action, may be efficiently used for the same complaints as acetyl-salicylic acid.

Derivative XIII is strongly analgesic and slightly sedative; it is preferably used for treating pain interfering with sleep or accompanied by agitation.

The preferred dose of the aforementioned derivatives is as follows:

Derivative No.	Oral Administration	Rectal Administration	Intramuscular Administration
IV	100–200 mg per dose 300–1000 mg per 24 hours	250 mg per unit 3 suppositories per day	400 mg per ampoule 1–2 per day
X	100 mg per dose 200 mg per day	200 mg per unit 3 suppositories per 24 hours	
XI	200 mg per dose 600 mg per day	300 mg per unit 3 suppositories per 24 hours	
XIII	100 mg per dose 4 doses per day	300 mg per unit 2–3 doses per 24 hours	300 mg per ampoule 1–2 per day

All these derivatives, in suitable doses, can be presented in tablets, capsules, and suppositories. The most soluble derivatives (e.g. IV and XIII) can be presented in injectable ampoules.

The following are some examples of pharmaceutical forms of drugs according to the invention:

1) Tablets:

Derivative No.	IV	X	XI
Polyvinylpyrrolidine	100 mg	100 mg	200 mg
Corn starch	Q.S. for	Q.S. for	Q.S. for
Talc	1 tablet	1 tablet	1 tablet
Stearate	150 mg	150 mg	150 mg

2) Capsules:

Derivative No.	IV	X	XI
Polyvinylpyrrolidone	100 mg	100 mg	200 mg
Corn starch	Q.S. for	Q.S. for	Q.S. for
Aerosil (Registered Trade Mark)	1 capsule	1 capsule	1 capsule

3) Suppositories:

Derivative No.	IV	X	XI
Water Q.S. for dissolving	250 mg	200 mg	300 mg
Semi-synthetic glycerides Q.S. for 1 suppository of approx. 2 g	"	"	"

4) Injectable Solution:

Derivative No.	IV	XIII
Distilled apyrogenic water	400 mg	300 mg
Q.S. for a 5-mg ampoule	"	"

TABLE I

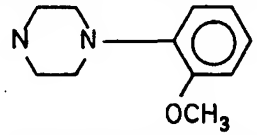
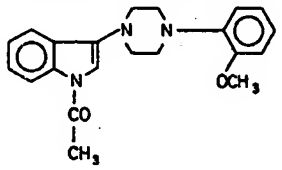
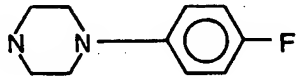
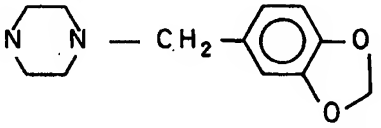
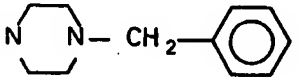
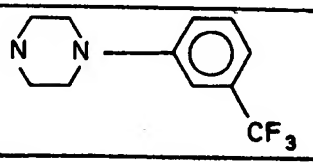
Compound No.	A	R_1	Piperazine Substituted by R_2	Structural Formula	Name
I	$CO-CH_3$ acetyl	H	 methoxyphenyl piperazine		1-acetyl 30 methoxy-phenylpiperazino indole
II	,,	,,			1-acetyl 3p.fluorophenyl-piperazino indole
III	,,	,,			1-acetyl 3-piperonyl-piperazino indole
IV	,,	,,			1-acetyl 3-benzyl piperazino indole
V	,,	,,			1-acetyl 3m.trifluoro-methylphenylpiperazino indole

TABLE I (Continued)

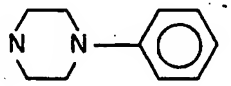
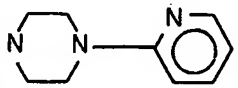
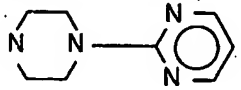
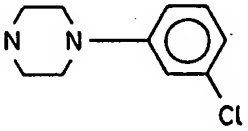
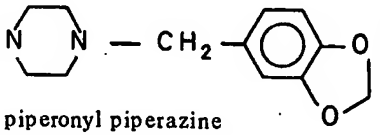
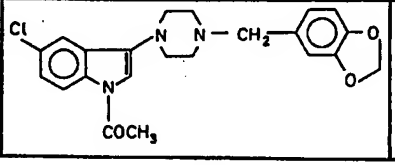
Compound No.	A	R_1	Piperazine Substituted by R_2	Structural Formula	Name
VI	$CO-CH_3$ acetyl	H			1-acetyl 3-phenyl-piperazino indole
VII	,,	,,			1-acetyl 3-pyridine piperazino indole
VIII	,,	,,			1-acetyl 3-pyrimidine piperazino indole
IX	,,	,,			1-acetyl 3m.chlorophenyl piperazino indole
X	,,	Cl	 piperonyl piperazine		1-acetyl 5-chloro 3-piperonylpiperazino indole

TABLE I (Continued)

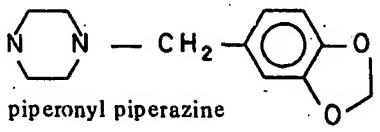
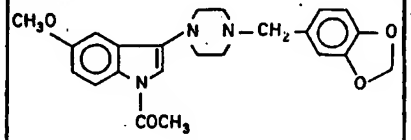
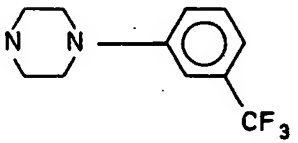
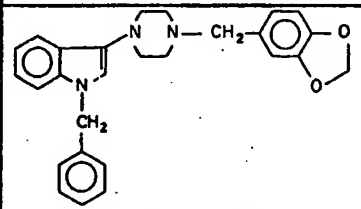
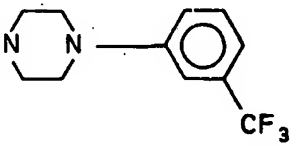
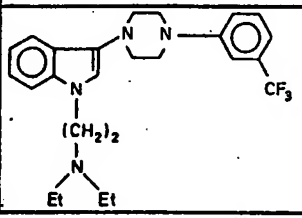
Compound No.	A	R_1	Piperazine Substituted by R_2	Structural Formula	Name
XI	CO–CH_3 acetyl	CH_3	 piperonyl piperazine		1-acetyl 5-methoxy-piperonylpiperazino indole
XIII	H	H	,,		3-piperonyl piperazino indole
XIV	,,	,,			3m.trifluoromethylphenyl-piperazino indole
XV	benzyl	,,	piperonyl piperazine		1-benzyl 3-piperonyl piperazino indole
XVI	N-diethyl-amino-ethyle	,,			1-N-diethylaminoethyl 3m.trifluoromethylphenyl-piperazino indole

TABLE I (Continued)

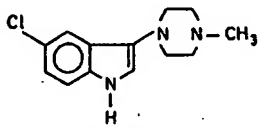
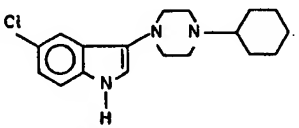
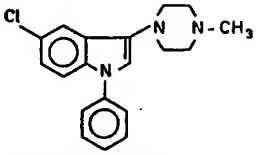
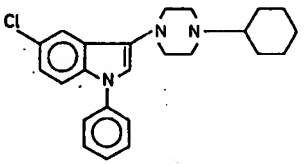
Compound No.	A	R_1	Piperazine Substituted by R_2	Structural Formula	Name
XVII	H	Cl		 methylpiperazine	5-chloro 3-methyl piperazino indole
XVIII	,,	,,		 cyclohexylpiperazine	5-chloro 3-cyclohexyl-piperazino indole
XIX	phenyle	,,		 methylpiperazine	1-phenyl 5-chloro 3-methyl piperazino indole
XX	,,	,,		 cyclohexylpiperazine	1-phenyl 5-chloro 3-cyclohexyl piperazino indole

TABLE II

Derivative No.	Yield	M.P. (°C)	IR (KBr)	Analysis
I	66%	*155° **220°	**2850, 2460, 1705, 1610 cm^{-1}	**$C_{21}H_{23}N_3O_2$, HCl = 385.9 C Calc. 65.36 Found 65.29 H 6.27 6.34 N 10.89 11.14
II	65%	**188°	**2850, 2360, 1700, 1615 cm^{-1}	**$C_{20}H_{20}ON_3F$, HCl = 373.8 C Calc. 64.25 Found 64.94 H 5.65 5.50 N 11.24 11.39
III	55%	**254°	**3100, 2400, 1685, 1610 cm^{-1}	**$C_{22}H_{23}N_3O_3$, HCl = 413.9 C calc. 63.84 Found 63.95 H 5.86 5.93 N 10.15 10.13
IV	46%	*114°	*2800, 2770, 1680, 1595 cm^{-1}	*$C_{21}H_{23}N_3O$ = 33.4 C Calc. 75.64 Found 75.02 H 6.95 6.65 N 12.60 12.86
V	70%	*148°	*2860, 1690, 1620 cm^{-1}	*$C_{21}H_{20}N_3OF_3$ = 387.4 C Calc. 65.10 Found 64.95 H 5.20 5.10 N 10.84 10.88
VI	51%	*146°	*2820, 1685, 1600 cm^{-1}	*$C_{20}H_{21}N_3O$ = 319.4 C Calc. 75.21 Found 74.98 H 6.63 6.59 N 13.16 13.45

TABLE II (Continued)

Derivative No.	Yield	M.P. (°C)	IR (KBr)	Analysis
VII	55%	*174°	*2840, 1680, 1600 cm^{-1}	*$C_{19}H_{20}N_4O$ = 320.4 C Calc. 71.22 Found 71.33 H 6.29 5.89 N 17.49 17.56
VIII	58%	*169°	*2820, 1715, 1590 cm^{-1}	*$C_{18}H_{19}N_5O$ = 321.4 C Calc. 67.26 Found 66.95 H 5.96 5.97 N 21.79 21.49
IX	58%	*158°	*3120, 2840, 1680, 1600 cm^{-1}	*$C_{20}H_{20}N_3OCl$ = 353.8 C Calc. 67.89 Found 66.90 H 5.70 5.79 N 11.87 11.77
X	40%	**252°	**1700 cm^{-1}	**$C_{22}H_{23}N_3O_3Cl_2$ = 438 C Calc. 59.00 Found 57.75 H 5.13 4.99 N 9.38 9.91
XI	45%	**232°	**1690 cm^{-1}	**$C_{23}H_{27}N_3O_4Cl_2$ (dichlorhydrate) = 480 C Calc. 57.5 Found 59.84 H 5.63 6.18 N 8.75 9.49
XVII	55%	*134 250**	**3250 cm^{-1}	**$C_{13}H_{16}N_3Cl$, HCl = 286 C Calc. 54.55 Found 54.28 H 5.44 5.77 N 14.68 15.12

TABLE II (Continued)

Derivative No.	Yield	M.P. (°C)	IR (KBr)	Analysis
XVIII	47%	*132 ***190	*3150 cm $^{-1}$	***$C_{18}H_{24}N_3Cl$, $C_4H_4O_4$ = 433.5 C Calc. 60.50 Found 60.80 H 6.46 6.58 N 9.68 9.61
XIX****	25%	*171	*2810, 1600 cm $^{-1}$	*$C_{19}H_{20}N_3Cl$ = 325.5 C Calc. 70.05 Found 70.45 H 6.11 6.24 N 12.90 13.12

* Base
** Hydrochloride
*** Monomaleate
**** Prepared by method similar to Example IX

TABLE III

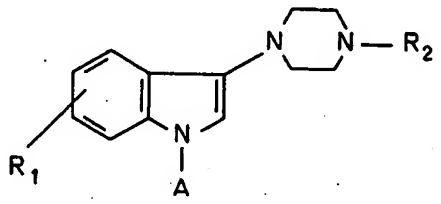
Derivative No.	LD_{50} P.O.	LD_{50} I.V.	Actimetry	Siegmund Test	Carrageenin oedema	Anti-serotonin (Harmine = 1)	Antipyretic activity AAS = 1 (aspirin)
I	1400	–	Stimulant 120	100	55	1/10	Inactive 100
II	1600	–	Inactive 400	400	45	1/5	Inactive 100
III	1400	–	Sedative 30	30	15	1	0.5
IV	1000	100	Sedative+ 20 min 80 Stimulant+ 2 h 100	18 + 1 h	100	2	Inactive 100
V	1600	–	Inactive 400	400	55	1/10	Inactive 100
VI	1600	–	Inactive 200	70 + 2 h	35	1/10	Inactive 100
VII	800	–	Inactive 200	40	40	1/2	Inactive 100
VIII	1600	–	Inactive 100	140	20	1/2	Inactive 100
IX	1600	–	Inactive 400	120	15	2	Inactive 100

TABLE III (Continued)

Derivative No.	LD_{50} P.O.	LD_{50} I.V.	Actimetry	Siegmund Test	Carrageenin oedema	Anti-serotonin (Harmine = 1)	Antipyretic activity AAS = 1 (aspirin)
X	1000	–	Sedative 120	18 + 1 h	30	2	Inactive 100
XI	1600		Sedative 80	45	75	1	2
XIII	800	75	Sedative 10	9 + 1 h	30	1	Inactive 100
XIV	1600	–	Inactive 400	250	30	2	2
XV	1200	–	Inactive 160	70	0	4	Inactive 100
XVI	1000	75	Sedative 400	150	55	2	Inactive 100

WHAT WE CLAIM IS:—

1. Piperazino-3-indoles having the following general formula:



wherein:

A is a hydrogen atom, a carboxylic acid radical or an alkyl, dialkylaminoalkyl, benzyl or phenyl group, which may or may not be substituted,

R_1 is a hydrogen or chlorine atom or an alkyl group having less than five carbon atoms, methoxy or hydroxy group, and

R_2 is an alkyl, benzyl or phenyl group or a cyclic or heterocyclic group, which may or may not be substituted.

2. Piperazino-3-indoles according to Claim 1, chosen from the 3-piperonylpiperazino indoles group.

3. Piperazino-3-indoles according to Claim 1, chosen from the group containing 3-alkylpiperazino indoles, 3-benzylpiperazino indoles, 3-phenylpiperazino indoles and 3-cyclohexylpiperazino indoles.

4. Piperazino-3-indoles according to Claim 2, chosen from the group containing:

1-acetyl 3-piperonylpiperazino indole,
1-benzyl 3-piperonylpiperazino indole,
1-acetyl 5-chloro 3-piperonylpiperazino indole,
1-acetyl 5-methoxy 3-piperonylpiperazino indole,
5-methyl 3-piperonylpiperazino indole, and
1-ethyl 3-piperonylpiperazino indole.

5. Piperazino-3-indoles according to Claim 3, chosen from the group containing:

1-acetyl 3-benzylpiperazino indole,
1-acetyl 3-O methoxyphenylpiperazino indole,
1-acetyl 3 m. trifluoromethylphenylpiperazino indole,
1-N diethylaminoethyl 3 m. trifluoromethylphenylpiperazino indole,
5-chloro 3-methylpiperazino indole,
5-chloro 3-cyclohexylpiperazino indole,
1-phenyl 5-chloro 3-methylpiperazino indole, and
1-phenyl 5-chloro 3-cyclohexylpiperazino indole.

6. A method of preparing piperazino-3-indoles according to any of Claims 1 to 5, comprising the step of reacting a 3-indolinone with a substituted piperazine in an inert solvent.

7. An anti-inflammatory, analgesic and antipyretic drug, having as the active substance a piperazino-3-indole according to any of Claims 1 to 5, or a salt thereof from a pharmaceutically acceptable acid.

8. A drug according to Claim 7 wherein the active substance is 1-acetyl 5-chloro 3-piperonylpiperazino indole hydrochloride.

9. A drug according to Claim 7 wherein the active substance is 1-acetyl 3-benzyl piperazino indole base.

10. A drug according to Claim 7 wherein the active substance is 1-acetyl 5-methoxy-3-piperonylpiperazino indole dihydrochloride.

11. A drug according to Claim 7 wherein the active substance is 3-piperonylpiperazino indole hydrochloride.

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